FIGURE 1

Examples of aqueous suspension compositions containing micrometer or submicrometer size particles of 9-nitrocamptothecin suitable for intravenous injection.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Sample Identification	9-Nitrocamptothecin (g)	Lipoid E80 (g)	Mannitol (g)	Trehalose (g)	Water (g)	Aq. Na Acetate* (g)	Batch size (g)	Diluent**	Dilution Factor	9-Nitrocamptothecin Concentration, mg/g	Lipoid E80 Concentration, mg/g	Mannitol Concentration, mg/g	Trehalose Concentration, mg/g	pH	Mean Size*** (m)	Size: 99.9% (m)
1-A	0.252	1.051	2.74		41.5	5.0	50.6	MAN**	2.5	1.99	8.3	55.0		5.6	1.93	6.52
1-B	0.253	1.001	2.75		41.1	5.0	50.1	MAN	2.5	2.02	8.0	55.0		5.7	1.02	2.47
1-C	0.250	2.001	2.76		40.0	5.0	50.0	MAN	2.5	2.00	16.0	55.0		5.8	0.96	2.44
1-D	0.259	2.510		6.0	36.3	5.0	50.0	TRE**	2.5	2.07	20.1		120.0	5.9	0.15	0.87
1-Ea	0.250	5.000		6.0	33.8	5.0	50.1	TRE	2.5	2.00	40.0		121.3	6.0	0.07	0.22
1-Eb								TRE	2.5	2.00	40.0		241.3	6.0	0.07	0.20
1-Ec								TRE	2.5	2.00	40.0		361.3	6.0	0.27	2.00
1-F	1.256	25.1		15.0	71.5	12.5	125.4	TRE	5.0	2.00	40.0		240.5	5.0	1.29	2.80
1-V		16.0		9.6	46.4	8.0	80.0	TRE	5.0		4.0		239.7	4.8	0.07	0.01

* Aq. Na Acetate: 20 mM sodium acetate solution in water with sodium hydroxide added to adjust pH to 5.0.

** Diluent: Aqueous solution containing mannitol (MAN) or trehalose (TRE) and sodium acetate in sufficient quantity to give the final concentration of sodium acetate of 2 mM and that of other ingredients as shown in columns 11-14 of Table 1.

*** Mean Size: Volume weighted mean particle diameter ($D_{4,3}$) in micrometers determined by a Malvern Mastersizer Microplus apparatus.

**** Size:99.9%: 99.9% of the particle population is smaller than this volume weighted particle diameter as determined by a Malvern Mastersizer Microplus apparatus.

FIGURE 2

Stability of an aqueous suspension formulation of 9-nitrocamptothecin stored at 4°C, 25°C, and 40°C for up to 170 days.			
Storage Temperature and Duration	Volume weighted particle diameter, micrometers		Appearance
	Mean	99.9 percentile	
Initial	1.29	2.80	Homogeneous yellow suspension, crystalline particles were observed in optical microscope under polarized light with a size distribution consistent with the measured size.
Stored at 4°C for 170 days	1.27	3.00	Small amounts of sediments were observed in the vial that were easily resuspendible to a homogeneous yellow suspension. Crystalline particles were observed in optical microscopic examination under polarized light with a size distribution consistent with the measured size. No agglomerates were found
Stored at 25°C for 170 days	1.20	2.91	
Stored at 40°C for 170 days	1.31	4.78	

FIGURE 3

IDD-D particle diameters in micrometers as a function of stress conditions.						
	Initial Particle Size	1. Stress Condition				
		Storage at 2-8°C	Storage at 20°C	Storage at 40°C	4-40°C Cycling	Shaking
Test Duration	Day 0	Day18	Day18	Day18	Cycle3	Day3
Mean (volume weighted)	0.20 µm	0.19 µm	0.18 µm	0.17 µm	0.19 µm	0.20 µm
99.9 Percentile	0.34 µm	0.34 µm	0.31 µm	0.31 µm	0.33 µm	0.33 µm

FIGURE 4

Protocol Design For First Melanoma Xenograft Study

Group	n	TreatmentRegimen1			
		Agent	mg/kg	Route	Schedule
1	10	NoTreatment	n/a	n/a	
2	10	IDD-P(1:3dilution)	n/a	iv	5/2/5
3	10	IDD-D(nodilution)	n/a	iv	5/2/5
4	10	D5Wwith3%DMA	n/a	po	Day1,4,8,11
5	10	CAMPTOSAR	100	ip	QWKx3
6	10	HYCAMTIN	10	ip	Q4Dx4
7	10	DTIC	150	ip	QDx5
8	10	9NC-IDD-P	3	iv	5/2/5
9	10	9NC-IDD-P	1.5	iv	5/2/5
10	10	9NC-IDD-D	2	iv	5/2/5
11	10	9NC-IDD-D	1	iv	5/2/5
12	10	9NC-D5W-3%DMA	4	po	Day1,4,8,11
13	10	9NC-D5W-3%DMA	2	po	Day1,4,8,11

FIGURE 5

Treatment Response Summary For First Melanoma Xenograft Study

Group	n	TreatmentRegimen				MDSto2.0g ±SEM(n)	Max.%BW Loss;Day	#Death [a]		#CR	#PR	#SD/PD
		Agent	mg/kg	Route	Schedule			TR	NTR			
1	10	NoTreatment	n/a	n/a		30.3 ± 4.4 (9)	---	0	0	0	0	1
2	10	IDD-P(1:3dilution)	n/a	iv	5/2/5	29.2 ± 2.5 (10)	---	0	0	0	0	0
3	10	IDD-D(nodilution)	n/a	iv	5/2/5	31.6 ± 3.2 (10)	-0.4%;Day27	0	0	0	0	0
4	10	D5Wwith3%DMA	n/a	po	Day1,4,8,11	26.0 ± 2.3 (8)	---	0	1	1	0	0
5	10	CAMPTOSAR	100	ip	QWKx3	47.3 ± 2.3 (9)	---	0	0	1	0	0
6	10	HYCAMTIN	10	ip	Q4Dx4	46.7 ± 2.6 (9)	---	0	0	1	0	0
7	10	DTIC	150	ip	QDx5	37.6 ± 4.0 (8)	-5.2%;Day5	1	0	1	0	0
8	10	9NC-IDD-P	3	iv	5/2/5	52.0 ± 0.6 (2)	-13.1%;Day13	3	0	1	3	1
9	10	9NC-IDD-P	1.5	iv	5/2/5	50.7 ± 3.4 (7)	-2.2%;Day5	0	0	2	0	1
10	10	9NC-IDD-D	2	iv	5/2/5	47.2 ± 3.6 (8)	---	0	0	1	1	0
11	10	9NC-IDD-D	1	iv	5/2/5	32.6 ± 2.3 (10)	---	0	0	0	0	0
12	10	9NC-D5W-3%DMA	4	po	Day1,4,8,11	45.3 ± 7.0 (3)	---	0	0	4	0	3
13	10	9NC-D5W-3%DMA	2	po	Day1,4,8,11	47.6 ± 3.4 (3)	---	0	0	4	1	2

[a] #Death:TR(TreatmentRelated);NTR(Non-TreatmentRelated)

FIGURE 6

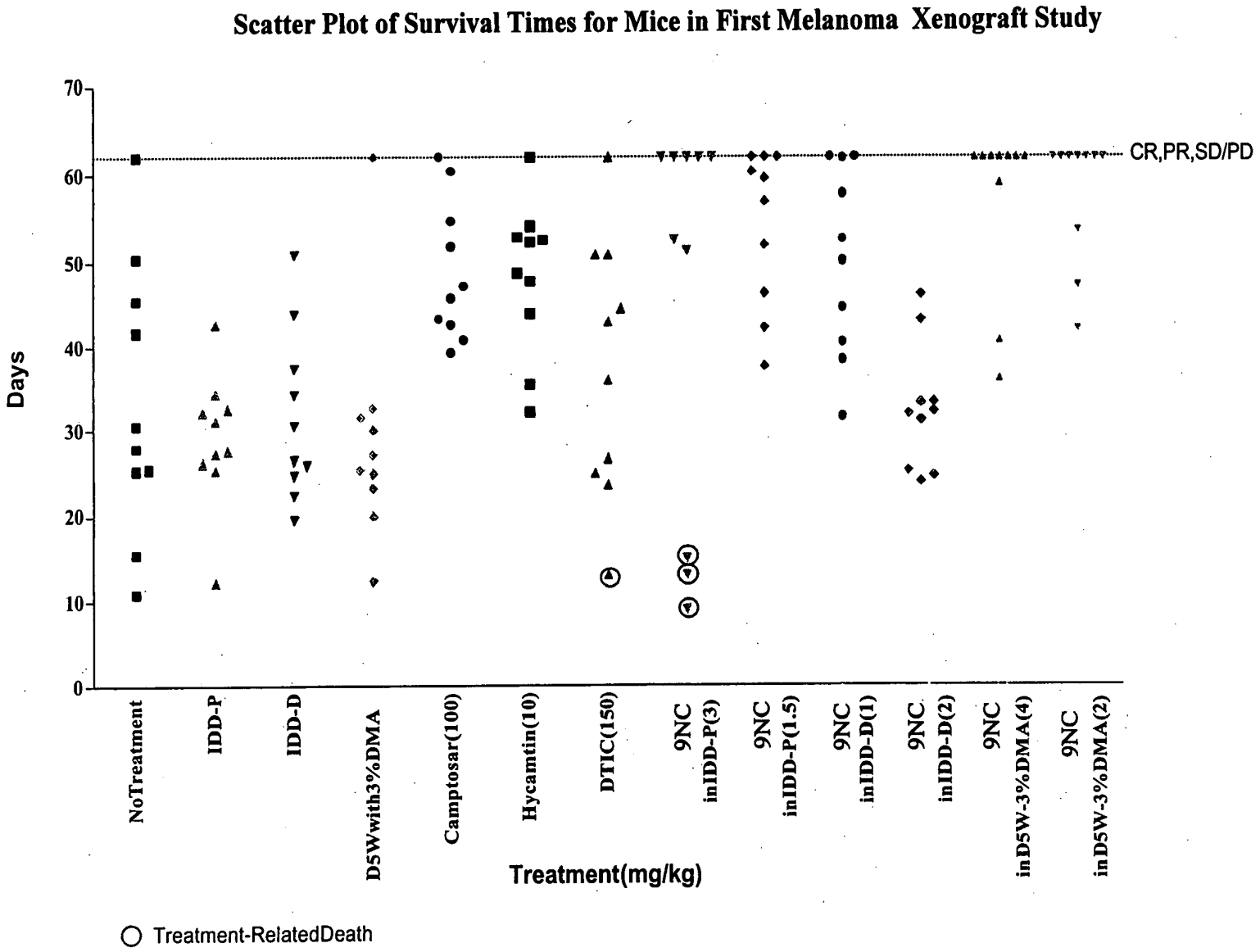
Scatter Plot of Survival Times for Mice in First Melanoma Xenograft Study
Days
70
60
50
40
30
20
10
0
CR,PR,SD/PD
NoTreatment
IDD-P
IDD-D
D5Wwith3%DMA
Camptosar(100)
Hycamtin(10)
DTIC(150)
9NC inIDD-P(3)
9NC inIDD-P(1.5)
9NC inIDD-D(1)
9NC inIDD-D(2)
9NC inD5W-3%DMA(4)
9NC inD5W-3%DMA(2)
Treatment(mg/kg)
Treatment-RelatedDeath

Figure 7

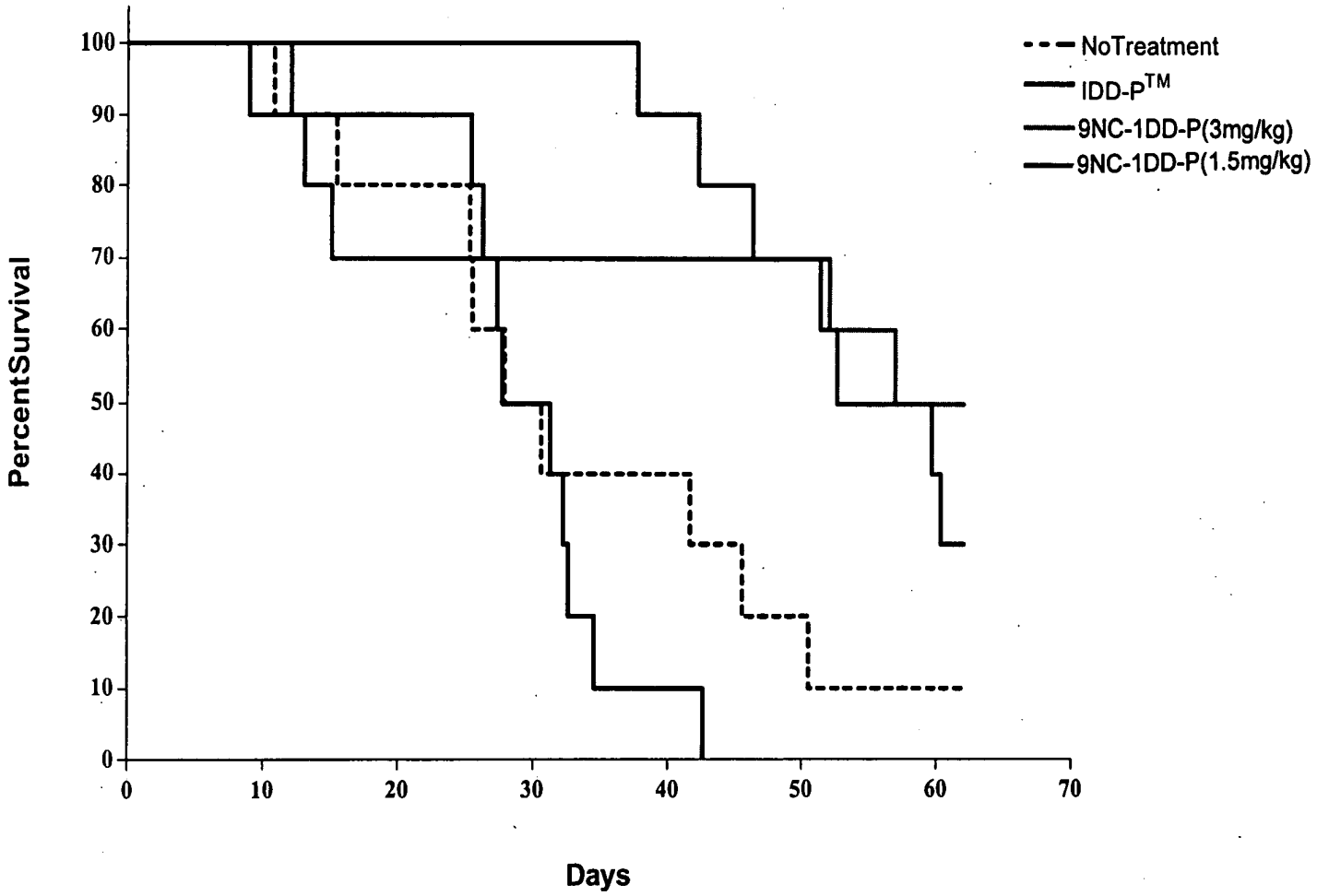

Figure 8

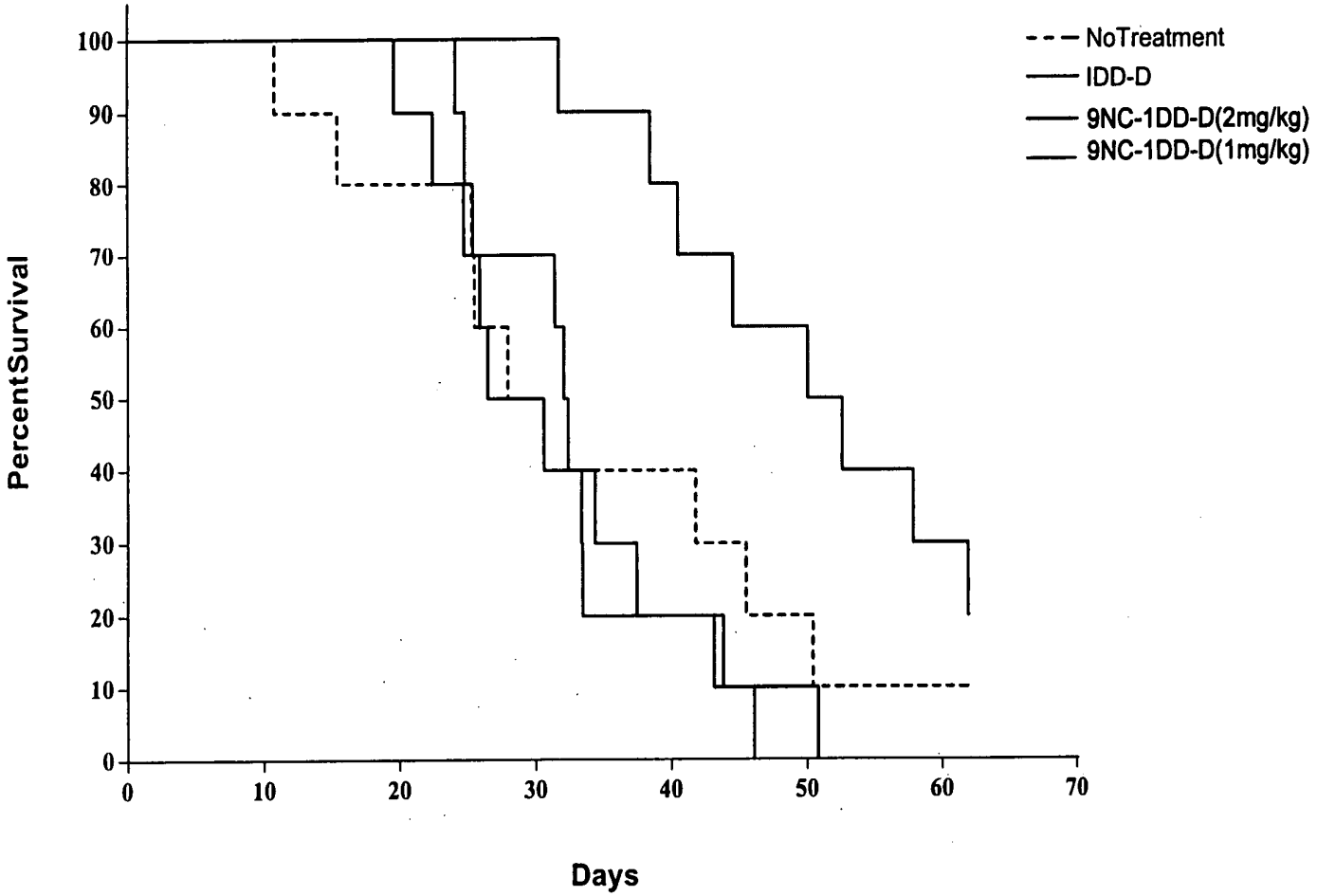
NoTreatment
IDD-D
9NC-1DD-D(2mg/kg)
9NC-1DD-D(1mg/kg)
PercentSurvival
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
Days

FIGURE 9

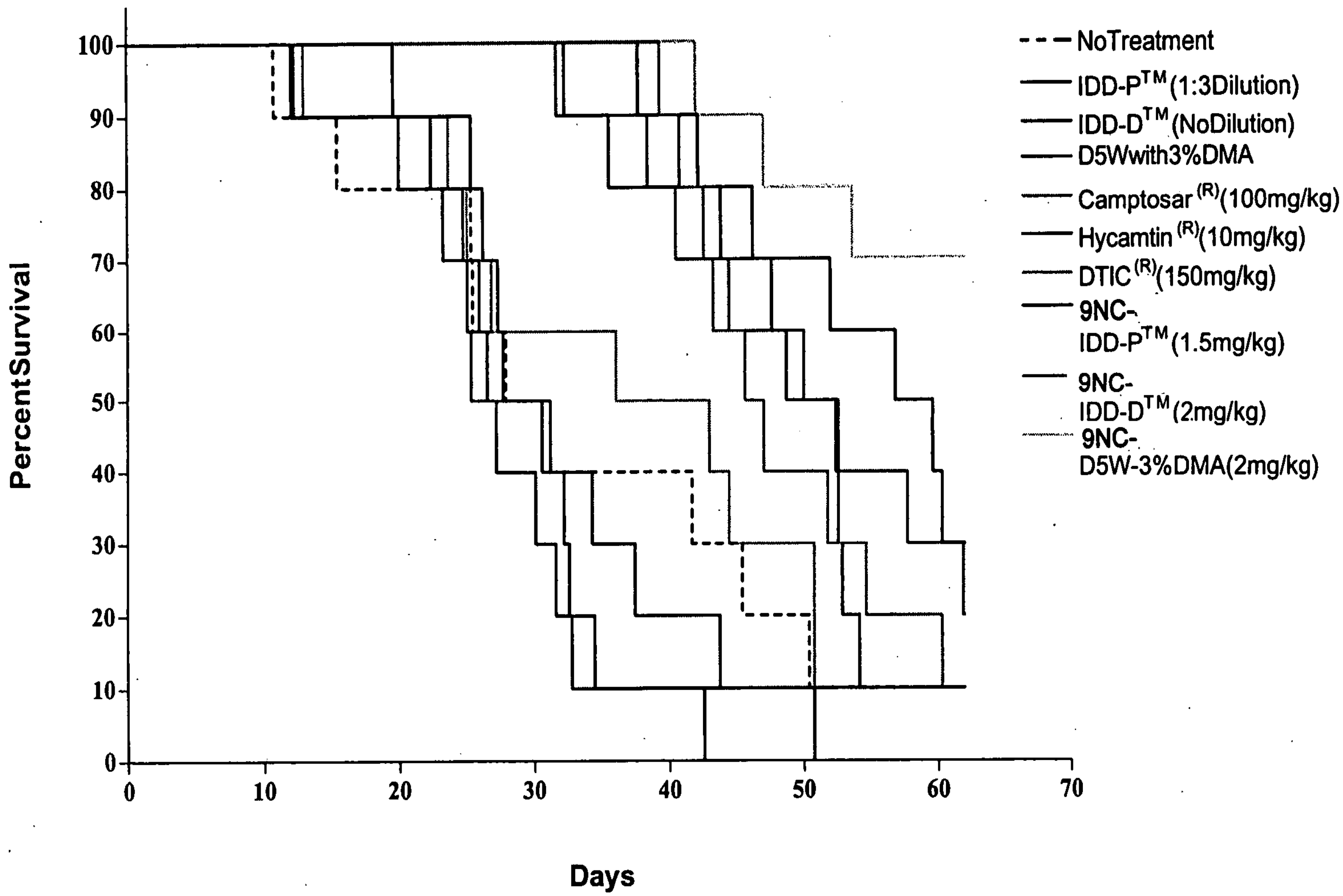

FIGURE 10

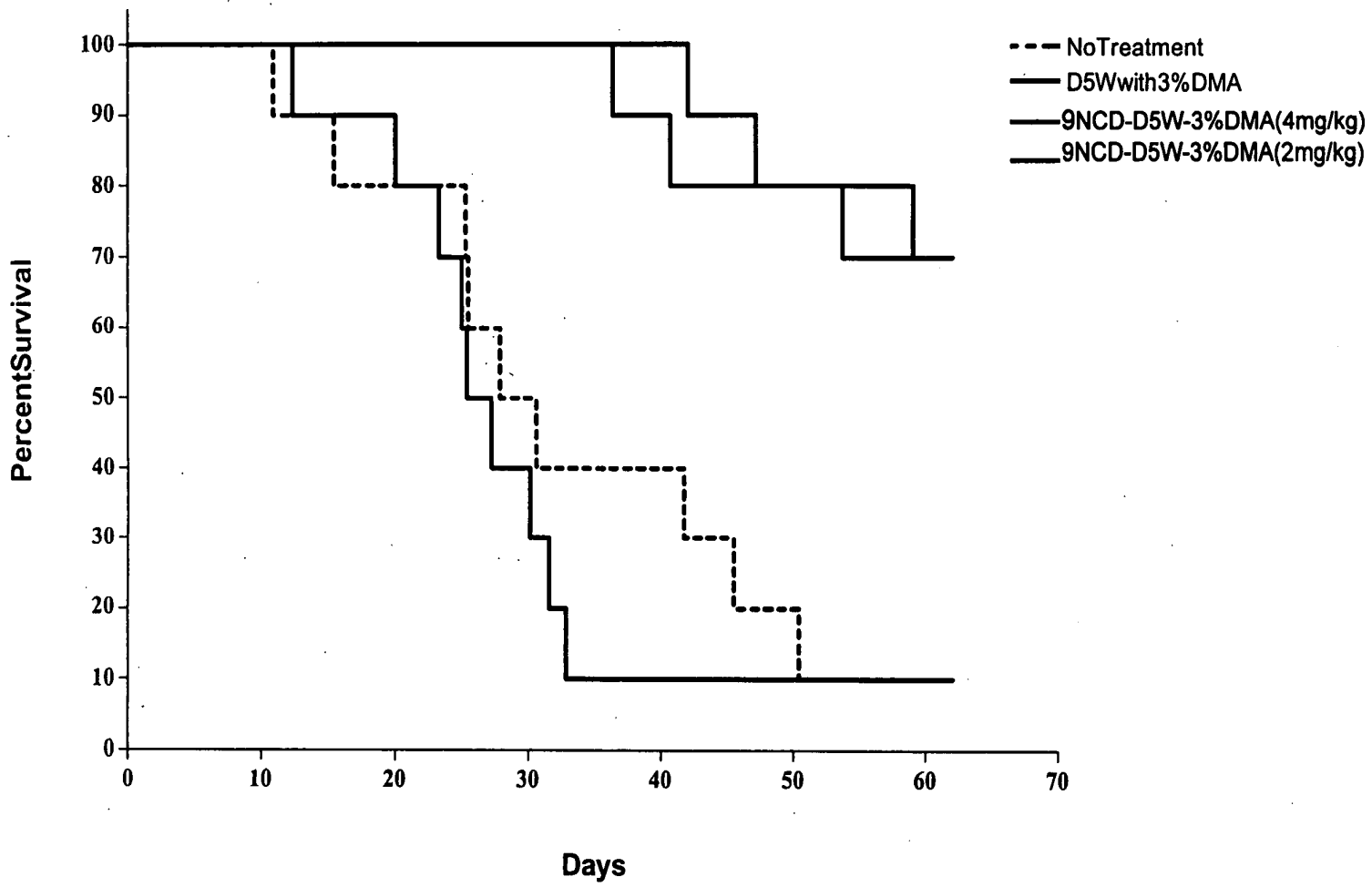

FIGURE 11

Treatment	Mean (days)	+/_ SEM	P vs no treatment	Initial n/n reaching 2 g or surviving to day 62
No treatment	20.5	3.0	---	10/10
IDD-P vehicle iv (5/2/5)	17.3	3.6	0.32	10/10
IDD-D vehicle iv (5/2/5)	18.0	5.4	0.48	10/10
D5W with DMA (5/2/5)	15.2	1.0	0.12	10/9
Camptosar 100mg/kg ip (Qwkx3)	39.7	3.2	0.0004	10/10
Hycamtin 10 mgkg ip (Q4Dx4)	39.9	2.9	0.0002	10/10
DTIC 150 mg/kg ip (QDx5)	31.3	4.6	0.06	10/9
9NC-in IDD-P 3 mg/kg iv	56.2	3.1	<<<0.0005	10/7
9NC in IDD-P 1.5 mg/kg iv	45.5	3.7	<<<0.0005	10/10
9NC in IDD-D 2mg/kg iv	41.9	3.1	<<<0.0005	10/10
9NC in IDD-D 1 mg/kg iv	26.1	1.4	0.11	10/10
9NC 4 mg/kg oral	54.1	3.8	<<<0.0005	10/10
9NC 2 mg/kg oral	54.6	3.1	<<<0.0005	10/10

5/2/5 + 5 daily dose, 2 days rest, 5 daily
Qwkx3 one dose per week for 3 weeks
Q4Dx4 four doses per day at four day intervals
QDx5 one dose per day for 5 days

FIGURE 12A

Group 1 of Second Melanoma Study

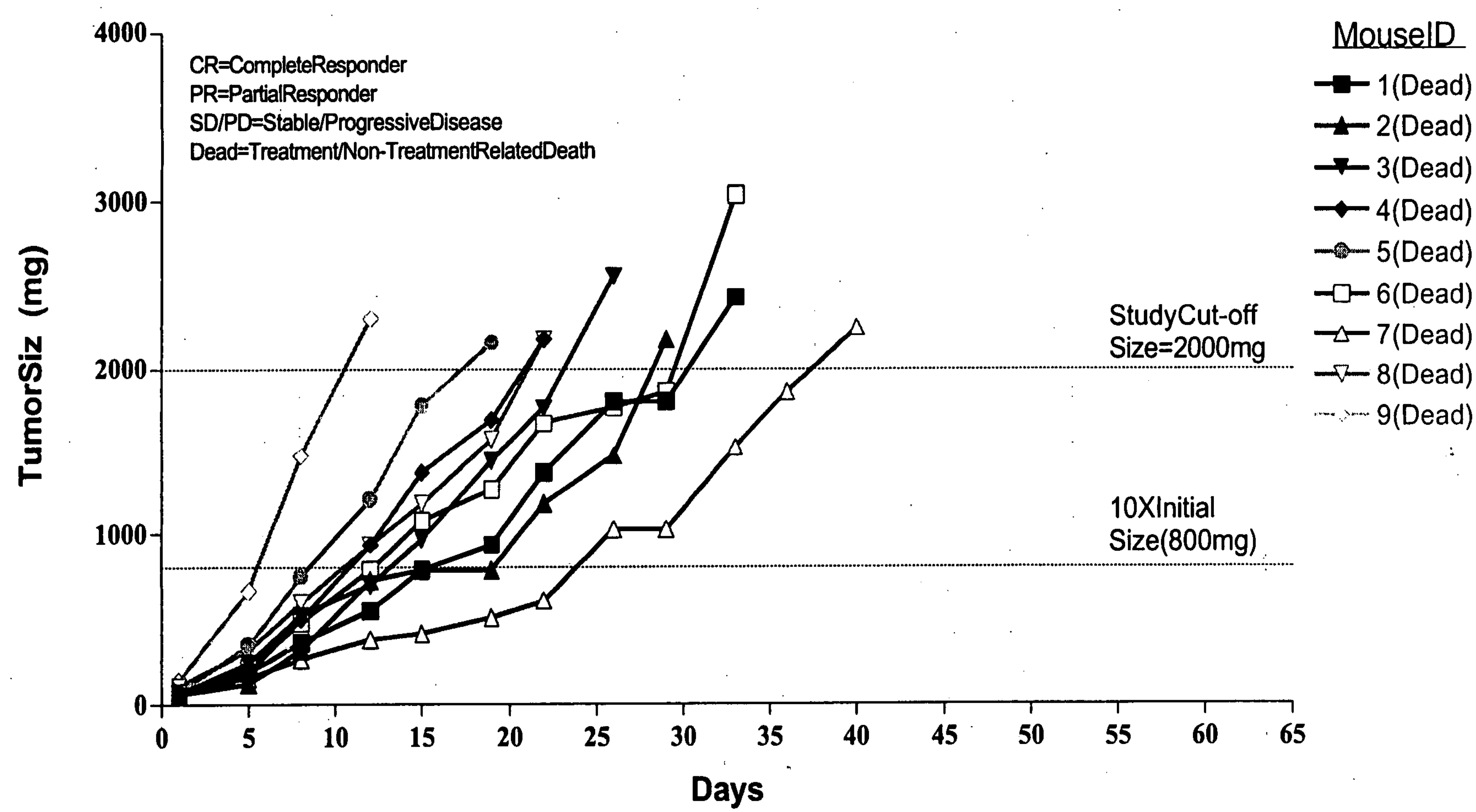

FIGURE 12B

Group 2 of Second Melanoma Study

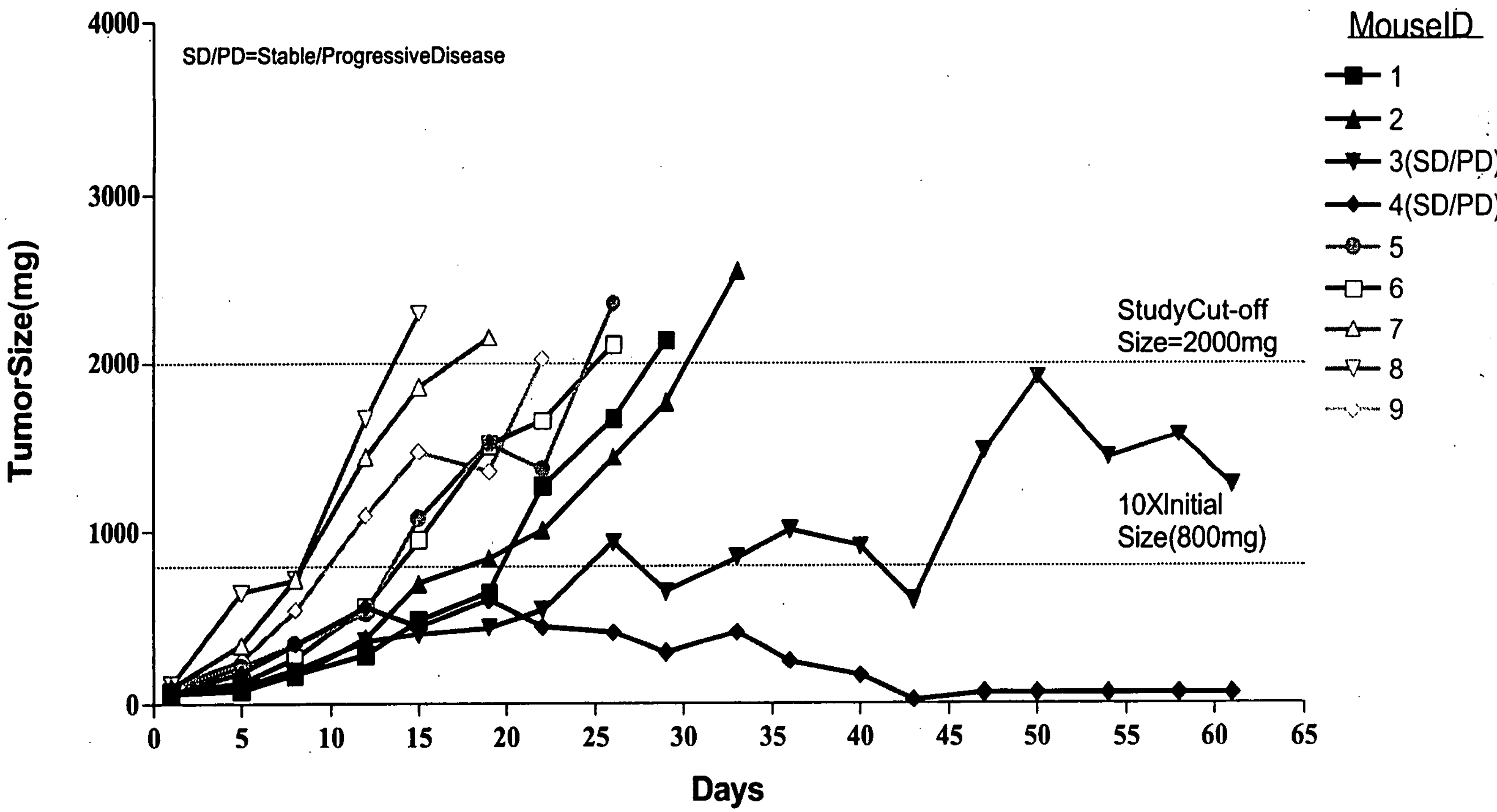

FIGURE 12C

Group 3 of Second Melanoma Study

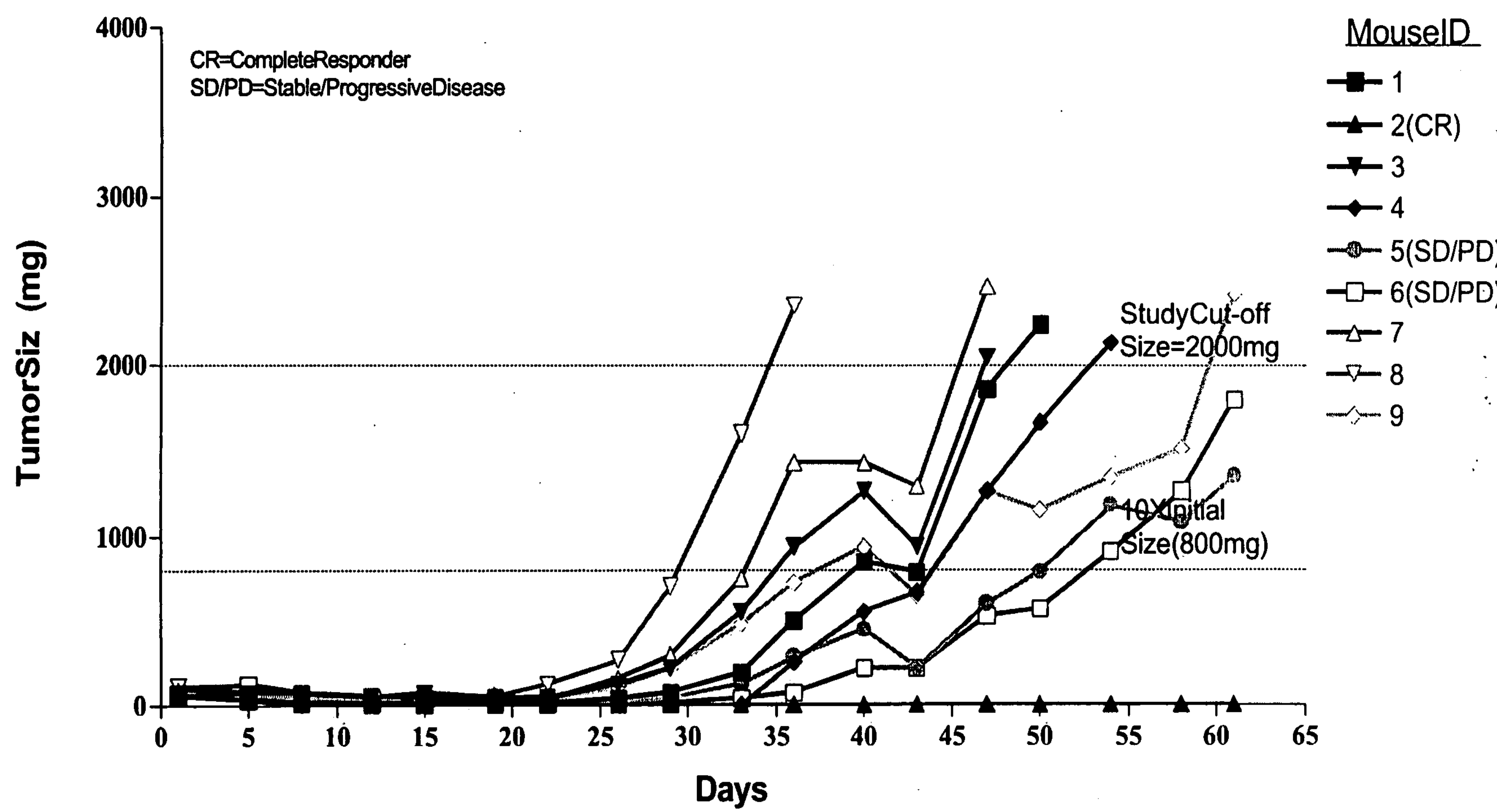

FIGURE 12D

Group 5 of Second Melanoma Study

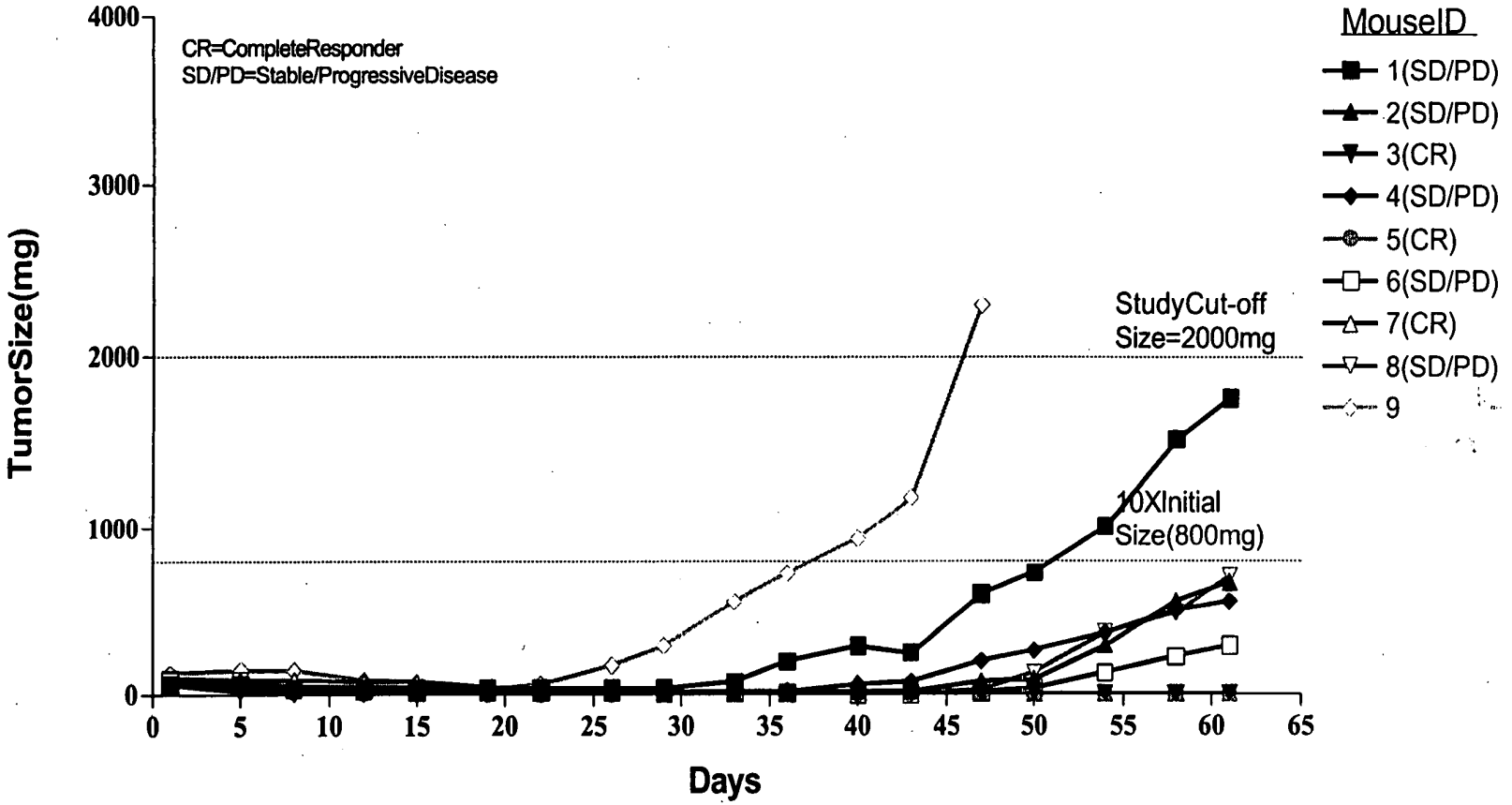

FIGURE 13

MX-1 Human Breast Cancer Xenograft Study

Treatment	Schedule	Mean Days to 10 X	S.E.M	P vs. no treatment	# of mice at start/ # mice reaching 10x
No treatment		17.4	2.23	--	10/10
IDD-P vehicle i.v.	5/2/5	16.5	1.1	n.s	10/10
9NC in IDDP 2.5 mg/kg i.v.	5/2/5	53.0	0.0	<<0.05	10/10
9NC in IDDP 1.75 mg/kg i.v.	5/2/5	53.0	0.0	<<0.05	10/10
9NC in IDDP 1.25 mg/kg i.v.	5/2/5	47.5	2.1	<<0.05	10/10.
Camptosar 100 mg/kg i.p..	QWK x 3	53.0	0.0	<<0.05	10/10
Hycamtin 10 mg/kg i.p.	Q4D x 4	53.0	0.0	<<0.05	10/10

FIGURE 14

Pan 1- Human Pancreatic Cancer Xenograft Study

Treatment	Schedule	Mean Days to 10 X	S.E.M	P vs. no treatment	# of mice at start/ # mice reaching 10x
No treatment		19.5	1.6	--	10/10
IDD-P vehicle i.v.	5/2/5	20.6	1.3	n.s	9/9
9NC in IDDP 2.5 mg/kg i.v.	5/2/5	34.3	2.0	<<0.05	10/10
9NC in IDDP 1.75 mg/kg i.v.	5/2/5	25.7	1.3	<0.01	10/10
9NC in IDDP 1.25 mg/kg i.v.	5/2/5	24.6	1.0	=.01	10/10.
Camptosar 100 mg/kg i.p..	QWK x 3	30.5	3.9	<0.05	10/10
Hycamtin 10 mg/kg i.p.	Q4D x 4	30.6	1.5	<<0.05	10/10

FIGURE 15

HT-29 Human Colon Cancer Xenograft Study

Treatment	Schedule	Mean Days to 10 X	S.E.M	P vs. no treatment	# of mice at start/ # mice reaching 10x
No treatment		26.9	2.0	--	8/8
IDD-P vehicle i.v.	5/2/5	29.4	1.6	n.s	8/8
9NC in IDDP 2.5 mg/kg i.v.	5/2/5	34.0	1.8	<0.05	8/8
9NC in IDDP 1.75 mg/kg i.v.	5/2/5	34.5	2.0	<0.05	9/9
9NC in IDDP 1.25 mg/kg i.v.	5/2/5	38.1	3.6	<0.05	9/9.
Camptosar 100 mg/kg i.p..	QWK x 3	35.7	2.2	<0.01	9/9
Hycamtin 10 mg/kg i.p.	Q4D x 4	34.4	1.5	<0.01	9/9

FIGURE 16

SKMES Human Lung Cancer Xenograft Study

Treatment	Schedule	Mean Days to 10 X	S.E.M	P vs. no treatment	# of mice at start/ # mice reaching 10x
No treatment		11.7	0.8	--	10/10
IDD-P vehicle i.v.	5/2/5	14.6	1.0	0.03	10/10
9NC in IDDP 2.5 mg/kg i.v.	5/2/5	27.3	1.6	<<0.05	10/10
9NC in IDDP 1.75 mg/kg i.v.	5/2/5	29.4	2.2	<<0.05	10/10
9NC in IDDP 1.25 mg/kg i.v.	5/2/5	35.2	5.7	<0.05	10/10.
Camptosar 100 mg/kg i.p..	QWK x 3	35.2	4.4	<<0.05	10/10
Hycamtin 10 mg/kg i.p.	Q4D x 4	33.6	3.6	<<0.05	10/10